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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/972,245
Filing Date: October 09, 2001
Appellant(s): ROBERTS ET AL.

Stephen A. Bent
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/10/06 appealing from the Office action mailed 12/29/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,531,122	Pederson (note that this name was misspelled as	3/2003

	"Peterson" throughout prosecution)	
4,678,812	Bollin et al	7-1987

Chinol et al (British Journal of Cancer 78(2): 189-197, 1998)

Deckert et al (Int. Journal of Cancer 87:382-390, 2000)

Alvarez et al (Med. Pediatr. Oncol. 34(3): 200-205, 2000)

Graham et al (Bone Marrow Transplant (21(9): 879-885, 1998)

Francis et al (Int. J. Hematol. 68(1): 1-18, 1998)

Roberts et al (J. Gen. Virol. 72:299-305,1991)

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Chinol et al (British Journal of Cancer 78(2): 189-197, 1998).

Chinol taught a method of assaying the effects on immunogenicity, pharmacokinetics and biodistribution of biochemical modifications to the polypeptide streptavidin. Streptavidin (M_r 66 kDa) was modified with monomethoxypolyethyelene glycol (mPEG) to varying extents (mean values of 3, 7, or 15 mPEG chains per polypeptide (see Table 1 on page 192). Each modified polypeptide was administered to a group of 5-6 subjects on days 0, 10, 16, and 51 in an excipient comprising 10 mM phosphate buffer. Blood was drawn from each subject on days 10, 16, 23, and 76 and tested for anti-avidin reactivity by ELISA. See section describing PEG conjugates bridging columns 1 and 2 on page 190; page 192, column 2, first full paragraph; and page 194, column 1, second and third full paragraphs. Anti-avidin reactivity is a measure of the antigenicity of the modified avidins, which in turn is considered to be a biological activity as recited in the claims. Pharmacokinetics and tissue distribution of each modified avidin were also measured. Chinol concluded that avidin modified with 7 mPEG chains was most suitable for therapeutic applications. See abstract. Pertinent to claim 9, Chinol taught that avidin is used in cancer therapy. See abstract.

Thus Chinol anticipates the claims.

Claims 1-3, 7, 9, 10, 17, 18, 41, 42, and 44 are rejected under 35 U.S.C. 102(a) as being anticipated by Deckert et al (Int. Journal of Cancer 87:382-390, 2000).

Deckert taught a method of assaying immunogenicity, pharmacokinetics and microdistribution of PEG-modified humanized A33 antibody. The A33 antibody is used to target colon cancer tumors. See title and abstract. A33 antibodies were modified

with 5kDa or 20 kDa methoxy-PEG-succinimidyl-succinate and administered to groups of 5 mice each in weeks 0, 1, 2, and 3. Blood was drawn in weeks 5, 9, and 13, and anti A33 antibody binding activity was assayed in the serum. See paragraph bridging pages 384 and 385, and Fig. 3 on page 385. This is taken as an indirect measure of a biological activity (antigenicity) of the modified A33 antibodies. So, Deckert taught a method in which differently pegylated antibodies are administered to subjects, followed by booster doses, and measures of antigenicity.

Thus Deckert anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez et al (Med. Pediatr. Oncol. 34(3): 200-205, 2000) in view of Graham et al (Bone Marrow Transplant (21(9): 879-885, 1998), and Francis et al (Int. J. Hematol. 68(1): 1-18, 1998).

Alvarez disclosed a comparative study of the effects of pegylated asparaginase relative to those of native asparaginase. Patients were given at least two doses of pegylated asparaginase. See Fig.1 on page 202. Pegylated asparaginase caused toxicity including nausea, vomiting and pancreatitis in greater than half of recipients

being treated for ALL. Patients were monitored by sequential serum amylase and lipase determinations. See abstract.

Alvarez did not teach the comparison of two different types of pegylated asparaginase.

Graham disclosed a clinical trial of pegylated asparaginase in the treatment of acute lymphoblastic leukemia (ALL). Patients received between 1 and 12 doses of pegylated asparaginase. Patients were monitored for relapse throughout the course of treatment. This is considered to amount to an assay of biological activity of the drug. Most of the patients who received the drug developed toxicities which resulted in abbreviated courses of administration. Symptoms included nausea, vomiting, and pancreatitis. See abstract. Evaluations of toxicity are also considered to be measurements of biological activity.

Francis taught that pegylation of protein drugs can cause can cause toxicity. See sentence bridging columns 1 and 2 on page 4, and first sentence of paragraph bridging pages 7 and 8. Francis also taught that bioactivity, stability, immunogenicity, and toxicity may be affected by the way in which a protein drug is pegylated. See abstract, and pages 2-4. Important considerations include the site of attachment of PEG, the degree of modification, the coupling chemistry chosen, the presence or absence of a linker, and generation of harmful co-products. See page 3, column 2, first full paragraph. Francis taught that the appropriate pegylation method is generally determined empirically by examining a range of different degrees of substitution, as well as different coupling techniques. See page 6, column 1, first full paragraph. The

bioactivity retention and other functions of the products may be assessed as a mixture, or individual members of a pegylation series may be assayed individually. See e.g. page 6, first full paragraph of column 1.

At the time the invention was made, pegylation of asparaginase was seen to have both advantages (increased half-life and reduced immunogenicity) and disadvantages (increased toxicity). It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a variety of differently pegylated versions of asparaginase, because Francis suggests that positive attributes of pegylated drugs can be maximized, while minimizing negative attributes, by determining the optimum pegylation conditions. See abstract. It would have been obvious to then compare and test the resulting pegylated forms of asparaginase to determine which drug was the best. It is clear that it was routine in the art to compare different forms of asparaginase in head to head studies in vivo as taught by Alvarez. It would have been similarly obvious to measure the effects of the drugs after each injection, as patients undergoing treatment for ALL, such as those in the Graham and Alvarez studies, are continuously monitored for disease progress. Claim 5 is included in this rejection because in light of the teachings of Francis, the extent of pegylation is a result-effective variable that is routinely optimized by those of skill in the art. See page 3, column 2, first full paragraph. Claim 6 is included in this rejection because the selection of different coupling chemistries is part of the optimization process suggested by Francis, and different chemistries result in different modifying agents. For example, in the TMPEG method discussed at page 5, the PEG is linked to the polypeptide directly

without any linker, whereas other chemistries may cause the introduction of immunogenic groups (see e.g. page 4, column 1, lines 1-10 of first full paragraph.

Thus the invention as a whole was prima facie obvious.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 above, and further in view of Pedersen et al (US Patent 6,531,122)

The teachings of Alvarez, Graham, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases. Francis also teaches that one reaction chemistry known in the art for PEG modification utilizes a cyanuric chloride linker. See page 4, lines 5-9 of first full paragraph.

These references did not teach SBA-, SC-, and ALD-PEGs.

Pedersen taught that SBA-, SC-, and ALD-PEGs, as well as a variety of other types of modified PEGs, including those with a cyanuric chloride linker, may be used interchangeably to modify polypeptide drugs. See paragraph bridging pages 24 and 25; column 25, first full paragraph, especially, lines 12, 27, 28, and 30; and column 26, lines 36-42.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify asparaginase with any of SBA-, SC-, and ALD-PEGs, because these derivatives were well known equivalents in the prior art. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted,

one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was prima facie obvious.

Claims 8, 11, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 above, and further in view of Roberts et al (J. Gen. Virol. 72:299-305,1991).

The teachings of Alvarez, Graham, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references did not teach an enzyme used to treat viral infection, used to reduce glutamine levels, or asparaginase glutaminase from *Pseudomonas*.

Roberts taught that glutaminase asparaginase from *Pseudomonas* can be used to treat retroviral disease by repeated administration, and that pegylation of the enzyme increases its half-life several fold. See abstract, and page 304, penultimate sentence of column 1.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify *Pseudomonas* asparaginase glutaminase by pegylation. One would have been motivated to do so in order to increase its half-life in vivo and to decrease its

immunogenicity, as taught by both Roberts and Francis. It would have been similarly obvious to optimize the pegylation conditions as taught by Francis. In doing so it would have been obvious to deliver differently pegylated forms of the enzyme in vivo over the course of treatment taught by Roberts. It would have been obvious to monitor the progress of the disease over the course of treatment in view of the teachings of Alvarez and Graham, who show that this is routine in the biomedical art.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alvarez, Graham, and Francis, as applied to claims 1-3, 5-7, 9, 10, 12, 13, 17, and 41-46 above, and further in view of Bollin et al (US Patent 4,678,812, issued 7/7/87).

The teachings of Alvarez, Graham, and Francis are summarized above and can be combined to render obvious methods of synthesizing and comparing differently pegylated asparaginases.

These references did not teach adding an excipient that protects asparaginase during lyophilization.

Bollin taught that proteins can be stabilized by lyophilization and that saccharides are useful in stabilizing asparaginase during lyophilization.

It would have been obvious to one of ordinary skill in the art to add saccharides to the pegylated asparaginases developed by the methods described above, for the purpose of stabilizing them during lyophilization. One would have been motivated to do so because Bollin teaches that proteins may be stabilized by lypohilization, and that asparaginase in particular is stabilized by addition of saccharides during lyophilization.

Thus the invention as a whole was prima facie obvious.

(10) Response to Argument

Appellant's arguments filed 11/10/06 have been fully considered but they are not persuasive.

I. Appellant considers the rejection over Chinol at pages 10 and 11 of the Brief. Appellant argues that Chinol does not disclose comparing the selected biological activity of said first modified therapeutic agent with the selected biological activity of said second modified therapeutic agent, the extent of modification, and the conditions for modification, that prevent host-mediated inactivation of the therapeutic agent. This is unpersuasive because Chinol measured antigenicity of the modified compounds multiple times after multiple administrations. See section describing PEG conjugates bridging columns 1 and 2 on page 190; page 192, column 2, first full paragraph; Fig. 2 on page 193; page 194, column 1, second full paragraph through paragraph bridging columns 1 and 2; and Fig. 3 on page 194. So, Chinol measured the same biological activity at several time points after several administrations of differently modified compounds. Presentation of the data in Figs 2 and 3, and discussion of it in the text amounts to a comparison of the biological activity (antigenicity). Note that the specification at paragraph 43 states "biological activity" means any cellular or physiological response or reaction that that agent causes, either directly or indirectly, and that the biological activity is not necessarily the same activity as the therapeutic benefit that the agent bestows upon the subject. As a result it is reasonable to interpret

"biological activity" to embrace antigenicity. Note also that the claims require that only one of the type of polymer, the extent of modification, and the condition for modification must differ between the two test agents. In this case the extent of modification differs.

Appellant points out that Chinol used an ELISA to determine the titer of antibodies produced against mPEG-modified avidins, and indicates that Chinol did not measure the biological activity of biotin binding by streptavidin. This is correct, but not evidence of a lack of anticipation. The rejected claims do not exclude antigenicity from the genus of biological activities that can be measured, and so in measuring antigenicity Chinol did measure a biological activity of the modified compound that is a species of the claimed genus of biological activities.

Applicants specific arguments regarding claims 42 and 44 are unpersuasive. Regarding claim 42, Applicant argues that Chinol fails to disclose comparing the biological activity of step (a) of said first modified agent with the selected biological activity of step (a) of said second modified agent. As discussed above, Chinol clearly does this, and concludes that avidin modified with 7 mPEG chains was most suitable for therapeutic applications. While Chinol does not explicitly choose between any two types of polymer, or any two linkage chemistries, Chinol does practice each of the active method steps required by the claims, i.e. steps a-e, and the "comparing" step of step 'f', and therefore anticipates the claims. Further, it is clear that Chinol did select a type of polymer (PEG), and conditions for modification, or the experiment could not have been performed. Because Chinol did not elect to change these variables based

on the outcome of the experiment, Chinol is considered to have selected them based on the outcome.

Regarding claim 44, Applicant argues that Chinol fails to disclose comparing the biological activity of step (a) of said first modified agent with the selected biological activity of step (a) of said second modified agent to determine relative bioavailability of the agents, and selecting the type of biocompatible polymer, extent of modification, and conditions for modification based on the comparison. This is unpersuasive because, Chinol did compare the biological activities as required, and so inherently determined the bioavailability of the agents according to the claim. Further, it is clear that Chinol did select a type of polymer (PEG), and conditions for modification, or the experiment could not have been performed. Because Chinol did not elect to change these variables based on the outcome of the experiment, Chinol is considered to have selected them based on the outcome.

II. With regard to the rejection over Deckert, Appellant argues at pages 11-13 of the Brief that Deckert does not disclose comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent after the modified agents have been administered to a subject. Appellant notes that the biological activity of step (a) is the same activity referred to in subsequent references to biological activity. Appellant argues that Deckert fails to disclose assaying a first or a second modified therapeutic agent after the first or second agent has been administered to a subject. This is unpersuasive. Deckert measured

antigenicity of differently modified A33 antibodies by detecting anti-A33 antibodies after multiple administrations of the modified A33 antibodies to a subject. See paragraph bridging pages 384 and 385, and Fig. 3 on page 385. Note that the claims do not require that the measurements must be made between administrations. So, the same activity, i.e. antigenicity of the modified antibody, was measured each time, and Deckert assayed the antigenicity of differently modified agents at multiple times after multiple administrations, thereby anticipating all the active method steps of the claims.

Appellant argues in the paragraph bridging pages 11 and 12 that the extent of pegylation to use was determined by in vitro studies measuring the acceptable loss of biological activity, and that in vivo studies were used only to find which modifications reduced immunogenicity. Appellant notes that the binding activity of A33 antibodies in vivo was not measured. These arguments are unpersuasive because the immunogenicity of the modified A33 antibodies is considered to be a biological activity, so in vivo studies *were* in fact used to assess a biological activity of differently modified A33 antibodies.

Appellant argues at page 12 that Deckert's in vivo experiments were not performed to determine the extent of modification, but rather to find whether the modifications reduced immunogenicity. This is unpersuasive, because as a necessary consequence of the assay, Deckert determined which extent of modification assayed (5kDa or 20 kDa) had a greater or lesser effect on a biological activity (i.e. antigenicity). See Figures 3 and 4.

Appellant points out that Deckert determined the titer of antibodies produced against the modified A33 antibodies, and indicates that Deckert did not measure the antigen binding activity of the modified antibodies. This is correct, but not evidence of a lack of anticipation. The rejected claims do not exclude immunogenicity from the genus of biological activities that can be measured, and so in measuring immunogenicity Deckert did measure a biological activity of the modified compound that is a species of the claimed genus of biological activities. Applicants specific arguments regarding claims 42 and 44 are addressed above. All of the active method steps of the claims are taught by the reference.

III. Appellant addresses the rejection over Alvarez in view of Graham and Francis at pages 13 and 14 of the Brief. At page 13, Appellant points out that independent claim 1 requires comparing biological activities of first and second modified therapeutic agents, and that these activates must be the same activity. In response the PTO notes that the same biological activity, i.e. immunogenicity of asparaginase was measured.

With specific regard to Alvarez. Appellants noted that Alvarez did not assay asparaginase with various extents of modification with PEG. In response, the PTO notes that Alvarez was not relied upon to do so. Alvarez and Graham were relied upon to show that pegylation of asparaginase was well known in the art at the time of the invention, that it was routine to test pegylated forms of asparaginase in vivo, and that it was well recognized that pegylated asparaginase caused variety of side effects such as toxicity including nausea, vomiting and pancreatitis. Francis was relied upon to show

that it was well known at the time of the invention that bioactivity, stability, immunogenicity, and toxicity may be affected by the way in which a protein drug is pegylated, such that one of ordinary skill in the art would clearly appreciate that it would be obvious to assay in vivo differentially pegylated forms of asparaginase to determine which form was the least toxic, as well as the most stable, most active, and least immunogenic.

Appellant argues at page 13 that Alvarez did not test a biological activity of asparaginase after first and subsequent injections. This is unpersuasive because it clearly would have been obvious to measure effects of the modified asparaginase such as toxicity, (particularly in view of the teachings of Alvarez and Graham),as well as bioactivity, stability, and immunogenicity in view of the teachings of Francis. Furthermore, making such measurements over the course of treatment would be obvious in view of the teachings of Alvarez and Graham who measured the disease process continually. Also, t was well known in the prior art that host mediated inactivation of protein drugs was a problem that led to reduced circulation time and reduced effectiveness, and that one of the purposes of pegylation was to reduce host mediated inactivation. See e.g. Francis (1998) page 2, column 1, second full paragraph, and following items 1, 2, 4, 5, and 6. It is apparent that one purpose of the Francis article is to show that the type of pegylation used affects such factors as retention of bioactivity, stability, and immunogenicity. See abstract. Therefore, it was obvious that one of the purposes for comparing differently pegylated proteins was to select conditions that minimized host-mediated inactivation.

Appellant argues at page 14 that the combined references do not teach step (f) of claims 44 and 45. This appears to be an argument that the references do not teach determination of the relative bioavailability of the modified agents. This is unpersuasive because the active method steps are all rendered obvious as discussed above. The intended use of performing the active method steps "to determine the relative bioavailability" of the two agents is considered to be accomplished if the active method steps (steps a-e) are accomplished. Steps a-e are considered obvious for the reasons set forth above. In any case, it would clearly have been obvious to select the modified asparaginase that was the least toxic, the most stable, the most active, and least immunogenic because toxicity, stability, and activity were all variables that were known in the prior art to be affected by pegylation (see Francis, above). Note that the claims do not explicitly require any measurement of bioavailability, and only require comparisons of biological activity.

At pages 15-18, Applicant applies the same arguments to the rejection of claim 4 over Alvarez, Graham, Francis and Pederson, to the rejection of claims 8, 11, and 20-22 over Alvarez, Graham, Francis and Roberts, and to the rejection of claims 18 an 19 over Alvarez, Graham, Francis and Bollin, adding only that the Pederson, Roberts, and Bollin references do not cure the deficiencies of the Alvarez, Graham, and Francis references. These arguments are unpersuasive for the reasons set forth above.

For these reasons, the rejections are considered proper and are maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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